NICE National Institute for Health and Care Excellence

2025 exceptional surveillance of ovarian cancer: recognition and initial management, colorectal cancer, and oesophago-gastric cancer: assessment and management in adults (NICE guidelines CG122, NG151 and NG83)

Surveillance report

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Contents

Surveillance decision

We will update the NICE guidelines on ovarian cancer: recognition and initial management, colorectal cancer and oesophago-gastric cancer: assessment and management in adults.

The update will focus on ensuring consistency between NICE products covering hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery (CRS) in line with the current evidence base.

For NICE's guideline on ovarian cancer, a link to NICE's interventional procedures guidance on cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis will be added to recommendation 1.4.2.1.

Further links will be added to recommendation 1.5.9 in NICE's guideline on colorectal cancer and section 1.4 in NICE's guideline on oesophago-gastric cancer.

Reason for the exceptional review

To examine the impact of the National Institute for Health and Care Research (NIHR) health technology assessment (HTA) on HIPEC and CRS for people with peritoneal metastases: a systematic review and cost-effectiveness analysis.

HIPEC with CRS is a treatment used for peritoneal carcinomatosis, when cancer has spread from its primary site, such as the ovaries or bowel. CRS involves a complex surgery, in which all macroscopic tumour is removed. Following the tumour removal, the abdominal cavity is filled with a heated chemotherapy solution for 30 to 120 minutes. This solution is drained before the abdominal cavity is closed.

NHS England's Clinical Commissioning Policy from April 2013 stated that CRS plus HIPEC can be routinely commissioned in the NHS for patients with peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma.

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Feedback from topic experts.
- Considering the evidence used to develop the guidelines.
- Considering relevant information from previous surveillance reviews of the guidelines.
- Examining related NICE guidance and quality standards.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

This study compared the relative benefits, harms, and cost-effectiveness of HIPEC plus CRS plus systemic chemotherapy (SC) versus CRS plus SC in people with peritoneal metastases from colorectal, gastric, or ovarian cancers. They conducted a systematic review, meta-analysis and a model-based cost-utility analysis.

The study authors searched MEDLINE, EMBASE, Cochrane library, and the Science Citation Index, ClinicalTrials.gov, and WHO ICTRP trial registers up to 14 April 2022. Eight randomised control trials (RCTs) were identified for inclusion, of these, 7 were included for the final analyses (955 participants). The comparisons in the trials were: HIPEC plus CRS plus SC versus CRS plus SC in the majority of trials and HIPEC plus CRS plus SC versus SC in the remaining 2 trials. Due to the limited evidence found, there was only 1 trial for the majority of comparisons, with the exception of stage III or greater epithelial ovarian cancer. The uncertainty in results was evaluated in the HTA using the GRADE methodology.

Within this publication, they also performed a model-based cost-utility analysis estimating mean costs and quality-adjusted life years per patient. Cost-effectiveness analyses were conducted for each of the comparisons stratified by the type of cancers in the systematic review. Costs were calculated from the NHS and personal social services perspective, and were discounted at the rate of 3.5% per annum. Cost-effectiveness was measured using net monetary benefits (NMBs). The option with the highest NMB represented better value for money.

Results for people with ovarian cancer

For people with ovarian cancer, HIPEC plus CRS plus SC probably decreases all-cause mortality compared to CRS plus SC (46.3% versus 57.4%; hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57 to 0.93). This evidence was from 3 trials with 500 participants; it was classed as moderate certainty evidence. For HIPEC plus CRS plus SC versus CRS plus SC, the incremental NMB at willingness to pay (WTP) of £20,000 and £30,000 was £46,761.81 and £71,938.23. This indicates that HIPEC plus CRS plus SC is cost-effective compared to CRS plus SC in the NHS.

This comparison resulted in little to no difference in health-related quality of life (mean difference [MD] 4.85; 95% CI -7.74 to 17.44; 1 trial; 71 participants; moderate certainty evidence). There was no reported difference in the overall number of participants who reported serious adverse events between the 2 therapeutic combinations in data from 2 trials (26.7% in HIPEC plus CRS plus SC versus 25.2% in CRS plus SC; rate ratio [RR] 1.06; 95% CI 0.73 to 1.54; 2 trials; 316 participants; moderate certainty evidence). However, it was also reported that HIPEC may increase the number of serious adverse events per participant (41.4 events per 100 participants in HIPEC plus CRS plus SC versus 32.6 events per 100 participants in CRS plus SC; RR 1.27; 95% CI 1.09 to 1.49; 1 trial; 184 participants; moderate certainty evidence).

Results for people with colorectal cancer

For people with colorectal peritoneal metastases, HIPEC plus CRS plus SC probably results in little to no difference in all-cause mortality compared to CRS plus SC (60.6% versus 60.6%; HR 1.00; 95% CI 0.63 to 1.58) and may increase the proportion of serious adverse events (25.6% in HIPEC plus CRS plus SC versus 15.2% in CRS plus SC; RR 1.69; 95% CI 1.03 to 2.77). This evidence was from 1 trial with 265 participants; it was classed as low certainty evidence. For this treatment comparison, the incremental NMB at WTP of £20,000 and £30,000 were -£6,162.83 and -£6,164.19 respectively, indicating that HIPEC plus CRS plus SC was not cost-effective compared to CRS plus SC in the NHS.

However, when HIPEC plus CRS plus SC is compared to SC alone it probably decreases all-cause mortality (40.8% versus 60.8%; HR 0.55; 95% CI 0.32 to 0.95). This evidence was from 1 trial with 105 participants and was classed as moderate certainty evidence. For this treatment comparison, the incremental NMB at WTP of £20,000 and £30,000 were £107,909.46 and £167,621.58 respectively, indicating that HIPEC plus CRS plus SC is cost-effective compared to SC alone in the NHS.

Results for people with gastric cancer

There was very limited evidence identified for people with gastric cancer, therefore the conclusions drawn should be interpreted with caution. For people with gastric cancer there was high uncertainty about the clinical effects of a HIPEC regime compared to a CRS regime. For this comparison, the incremental NMB at WTP of £20,000 and £30,000 were £14,174.73 and £22,955.89 respectively for HIPEC plus CRS plus SC versus CRS plus SC. Indicating that HIPEC plus CRS plus SC is cost-effective compared to CRS plus SC in the NHS.

However, HIPEC plus CRS plus SC probably decreases all-cause mortality compared to SC alone (40.8% in HIPEC plus CRS plus SC versus 100% in SC alone; minimum follow-up 24 months; HR 0.40; 95% CI 0.30 to 0.52; 1 trial; 17 participants; moderate certainty evidence). For this comparison, the incremental NMB at WTP of £20,000 and £30,000 were £81,796.38 and £127,768.23 respectively for HIPEC plus CRS plus SC versus SC. Indicating that HIPEC plus CRS plus SC is cost-effective compared to SC alone in the NHS.

Topic expert feedback

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We contacted 16 people, and got 6 responses. Responses were received from 3 consultant oncologists, 2 colorectal surgeons, and 1 primary care doctor.

We wanted to know whether topic experts were aware of HIPEC with CRS being used in the NHS for any of the above populations. Five out of the 6 topic experts who responded said that they were aware of it being used in hospitals in the UK. Multiple locations spread across the country were mentioned by them. They were aware of HIPEC being used for patients with colorectal cancer and ovarian cancer. One topic expert mentioned that they were aware that it is being looked at in gastric cancer but stated that there was no defined role in this indication.

We also asked topic experts if they were aware of any ongoing research in this area. One topic expert highlighted the Pressurised IntraPeritoneal Aerosolised Chemotherapy (PIPAC) for the treatment of colorectal peritoneal metastases study. We plan to regularly check whether this study has published results and evaluate the impact of the results against current recommendations as soon as they are published.

In additional comments, 1 topic expert said that they did not believe that the evidence base for HIPEC was markedly superior to conventional intravenous chemotherapy. They reference the CHIPOR study (Classe et al. 2023), which found that HIPEC resulted in increased overall survival (54.3 months; 95% CI 41.9 to 61.7; versus 45.8 months; 95% CI 39.9 to 54.2; p=0.02). However, there was no difference in overall progression free survival, and an increase in grade 3 and 4 adverse events.

Information considered when developing the guidelines

Ovarian cancer

The use of HIPEC was not discussed during the development of the NICE guideline on ovarian cancer in 2011. However, a review question was written asking whether, for people with ovarian cancer, intraperitoneal chemotherapy is effective in primary management? As a result of this evidence review, recommendation 1.4.2.1 states that you should not offer intraperitoneal chemotherapy to people with ovarian cancer, except as part of a clinical trial.

Intraperitoneal chemotherapy is chemotherapy delivered through an access port into the intraperitoneal space. It is typically delivered as an adjuvant treatment, following primary cytoreductive surgery. It is different from HIPEC because the chemotherapy agents are not heated before they are delivered, and the procedure is done via a port, and not during a surgical procedure.

The evidence for intraperitoneal chemotherapy came from 2 systematic reviews (1 containing 7 RCTs and the other containing 8 RCTs) that were considered high quality, and 1 RCT. All studies used the comparison of standard intravenous chemotherapy. Together, the evidence from 8 RCTs indicated that adjuvant intraperitoneal chemotherapy can significantly reduce the risk of death and of disease recurrence for up to 5 years of follow-up. There were however significant adverse effects associated with the procedure, with incidence of pain, fever, fatigue, hearing loss, infection and gastrointestinal and metabolic effects occurring up to 8 times more frequently in women receiving intraperitoneal chemotherapy. Cardiovascular events were not found to be different between treatment arms, however, and it was not possible to draw conclusions about the incidence of haematological, pulmonary, renal and neurological adverse effects, due to poor data quality. Health-related quality of life was reported in 1 trial to be significantly lower in the

short term following intraperitoneal chemotherapy, but these differences did not persist at 1 year of follow-up.

Though the evidence was assessed as high quality using GRADE, committee members highlighted that the studies investigated historical drug regimens and did not investigate intraperitoneal administration of drugs given intravenously in standard UK regimens at the time of development. Taking into consideration the increased toxicity and adverse events associated with intraperitoneal chemotherapy, the guideline development group did not feel able to recommend the use of intraperitoneal chemotherapy outside of clinical trials.

Colorectal cancer

During guideline development in 2020, evidence was assessed for the optimal combination and sequence of local and systemic treatments in patients presenting with metastatic colorectal cancer isolated in the peritoneum. As a result of this evidence review, recommendation 1.5.9 was written which states:

For people with colorectal cancer metastases limited to the peritoneum:

- offer systemic anti-cancer therapy **and**
- within a multidisciplinary team, discuss referral to a nationally commissioned specialist centre to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).

Two RCTs were identified that looked at the use of HIPEC plus CRS and SC. One RCT compared CRS plus HIPEC plus oxaliplatin to CRS only (the PRODIGE 7 trial Quenet et al. 2018) and the other RCT compared CRS plus HIPEC plus SC to CRS plus SC (Verwaal et al. 2003; Verwaal et al. 2008). The evidence was considered low quality, or very low quality for all outcomes.

The evidence for CRS and HIPEC was mixed. In the PRODIGE 7 trial, overall survival rates for all patients were higher than expected (both arms also received CRS), which was interpreted by the committee as evidence that high quality surgery is beneficial for survival outcomes. This is reflective of the cost-effectiveness results reported in the HTA report, which found that HIPEC plus CRS plus SC was not cost-effective compared to CRS plus SC; however, it was found to be cost-effective compared to SC alone. Current NICE guidance is for SC as standard, with consideration of referral for CRS plus HIPEC.

There was no clinically important difference in 5-year overall survival between those receiving a HIPEC regime, compared to those receiving surgery alone in the PRODIGE 7 trial. In the studies conducted by Verwaal et al., a clinically important increase in 2-year overall survival was seen for those whose treatment included CRS plus HIPEC plus SC, compared to CRS plus SC. In both trials, there was no difference in treatment related mortality between the treatment comparisons.

The PRODIGE 7 trial also reported an increased risk of complications associated with the use of HIPEC, compared to CRS alone. The committee noted that the doses of oxaliplatin used in the PRODIGE 7 trial are much higher than those used in the UK and could explain the high level of toxicity in the treatment arm (HIPEC plus CRS plus oxaliplatin versus CRS alone). While lower doses of oxaliplatin are used in the UK, this drug still has a risk of severe toxicity.

Based on the evidence and their clinical expertise, the committee made a consider recommendation for referral to a nationally commissioned specialist centre where CRS with HIPEC should be discussed within a multidisciplinary team. The committee made the recommendation in line with NICE's interventional procedures guidance on cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis.

Gastric cancer

During development of NICEs guideline on oesophago-gastric cancer in 2018, a review question was written asking what is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for gastric cancer? During the review, intraperitoneal chemotherapy was compared to surgery alone and to systemic chemotherapy. Both normothermic and hyperthermic intraperitoneal chemotherapy were considered.

For both comparisons the overall survival was greater for intraperitoneal chemotherapy compared with surgery alone and intravenous chemotherapy. However, the committee felt that these results should be interpreted with caution, in view of the recruited populations which were all from Japan or the Far East and so did not reflect the UK population, and the intravenous chemotherapeutic agents used, which do not represent current UK regimens. Given the uncertain benefit of intraperitoneal chemotherapy, a recommendation for research was therefore written in the full guideline: What is the role of intraperitoneal chemotherapy following surgical resection for gastric cancer?

Information considered in previous surveillance of the NICE guidelines

Ovarian cancer

The NICE guideline on ovarian cancer does not mention HIPEC. In relation to intraperitoneal chemotherapy, which was the focus of a review question during guideline development, there was an evidence update (January 2013). This evidence update identified 1 systematic review that indicated intraperitoneal chemotherapy had higher overall survival and progression free survival than intravenous chemotherapy. This is an updated version of a review included in the guideline and the conclusions do not substantially differ to the original ones. The evidence is unlikely to impact on the guideline.

The surveillance review conducted in 2016 found new evidence from 1 RCT that compares intravenous to intraperitoneal cisplatin/paclitaxel. The RCT reports no difference between the 2 groups, and the new evidence did not impact the guideline recommendations.

Colorectal cancer

There has been no surveillance completed for the section in the guideline on management of people with metastatic colorectal cancer in the peritoneum.

Gastric cancer

There has been no surveillance completed for the section in the guideline on radical treatment.

Other relevant NICE guidance

There is NICE's interventional procedures guidance on cytoreductive surgery followed by HIPEC for peritoneal carcinomatosis. The guidance covers peritoneal carcinomatosis resulting from the regional spread of gastrointestinal, gynaecological and other malignancies.

The rapid evidence review conducted for the interventional procedures guidance looked at 6 meta-analyses, 3 systematic reviews and 1 randomised controlled trial. The committee

discussed this evidence, alongside 2 commentaries from patients who have had this procedure. The interventional procedures guidance states that the evidence on the safety of CRS with HIPEC for peritoneal carcinomatosis shows frequent and serious but well-recognised complications. It also states that the evidence on its efficacy is limited in quality. Therefore, the interventional procedures guidance states that it should only be used with special arrangements for clinical governance, consent, and audit or research. The patient selection should be done by an experienced multidisciplinary team, and in highly specialised centres by clinicians with specialist expertise and specific training in CRS and HIPEC.

Equalities

Topic experts were asked about any equalities issues surrounding the use of HIPEC. One topic expert highlighted that older and more frail people may not benefit from HIPEC as it is not clinically appropriate for this population.

An equalities and health inequalities assessment was completed during this surveillance review. See appendix A for details.

Overall decision

NICE's guidelines on ovarian cancer, colorectal cancer and oesophago-gastric cancer will be updated.

In the NICE guideline on ovarian cancer, recommendation 1.4.2.1 states that you should not use intraperitoneal chemotherapy except as part of a clinical trial. This recommendation was written in 2011. The HTA that triggered this exceptional surveillance review found a survival benefit of HIPEC plus CRS plus SC compared to CRS plus SC in this population, indicating that the evidence base has changed since the recommendation was written.

The NICE guideline on colorectal cancer recommends that HIPEC plus CRS should be considered. This recommendation differs from the HTA, which found that HIPEC plus CRS plus SC probably results in little to no difference in all-cause mortality compared to CRS plus SC. Both the guideline and the HTA looked at the evidence from the PRODIGE 7 trial however, highlighting that the evidence for this population is not conclusive in one direction.

The NICE guideline on oesophago-gastric cancer does not make recommendations on HIPEC, but the committee did write a recommendation for research. The HTA did not find conclusive evidence in this population.

CRS plus HIPEC is commissioned within the NHS for patients with peritoneal carcinomatosis secondary to colorectal carcinoma, gastric carcinoma, pancreatic carcinoma and ovarian carcinoma. This policy was written in 2013, to coincide with NICE publishing their interventional procedures guidance in this area. Topic experts highlighted that the use of HIPEC is becoming more widespread, and that hospitals are taking active steps to set it up.

Currently NICE has an interventional procedures guidance that covers the use of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis in these populations. This guidance states that the technology should only be used with special arrangements. The evidence base has not changed substantially from when the interventional procedures guidance was written. The current evidence on efficacy of HIPEC with CRS is mixed, showing some survival benefit, while the evidence on the complications is well known. Given the small and evolving evidence base, recommendations for this intervention should be aligned with the interventional procedures pathway. Current recommendations in the guidelines are not reflective of the interventional procedures guidance, therefore, incorporation of the interventional procedures guidance into the guidelines should be conducted so that the information is consistent across NICE guidance.

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